Growth hormone in children (for growth hormone deficiency, Turner's syndrome, chronic renal failure and idiopathic short stature)

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the use of growth hormone treatment in children with growth hormone deficiency (GHD), Turner's syndrome (TS), chronic renal failure (CRF) and idiopathic short stature (ISS).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised primarily pre-pubertal boys and girls (age range: 1 - 13 years) with GHD, CRF, TS or ISS. Children with skeletal dysplasia (achondroplasia, Prader-Willi, Noonon, Russell-Silver) and those with intrauterine growth retardation were excluded from the review.

Setting
The setting was not stated, but it was likely to have been primary care or the community. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were derived from published studies dating from 1987 to 1995. The prices were derived from the British National Formulary 1995.

Source of effectiveness data
The effectiveness data were derived from a systematic review of the literature.

Outcomes assessed in the review
Height gain was the primary outcome measurement in this review. A variety of measures were employed in the reporting of this outcome, such as changes in standard deviation score (SDS), height change and height velocity per year. Other outcomes included psychological, academic and behavioural measures. Adverse events were also considered.

Study designs and other criteria for inclusion in the review
The inclusion criteria were not stated. The included studies comprised randomised controlled trials (RCTs), a controlled trial and case series.
Sources searched to identify primary studies
The authors searched MEDLINE (from 1985 to May 1996), HealthPLAN (from 1985 to December 1995) and GEARs, and also consulted a local expert in order to identify primary studies.

Criteria used to ensure the validity of primary studies
The grading and reporting of studies as "best quality" was based on several criteria. Specifically, the type of trial, the number of patients, patient accountability, focus of the trial and relevance of the outcomes.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Twenty-eight studies were included in the review. There were 8 RCTs, 1 controlled trial and 19 case series.

Methods of combining primary studies
The studies were combined in narrative form, according to the respective clinical condition.

Investigation of differences between primary studies
The authors provided a narrative account of differences between the primary studies. In particular, the difficulty in comparing height gain results from studies using different outcome measures was identified.

Results of the review
The authors reported that height improvements were observed in all treated children (regardless of disorder) when compared with their expected gain without treatment. The results were reported selectively by reference to 5 studies that were claimed to provide the "best quality" evidence as follows.

In terms of height gain, children (including pubertal patients) treated for GHD achieved a mean of 2.6 SD over an average of 5 years. Their initial height ranged from -6.2 SD to -2.9 SD and their final height from -1 SD to -3.3 SD.

Children treated for TS achieved a mean gain of 8.1 cm (3.2 inches) over original projections over a 5-year treatment period. Their original height was 143.8 cm (4 foot 8 inches) and the mean final height was 151.9 cm (5 foot).

Children treated for CRF achieved a mean gain of 1.48 SD in comparison with no treatment over a 2-year period. The initial height of the children was -2.94 SDS (control group -2.82 SDS) and the final height was -1.55 SDS (control group -2.91 SDS).

Treated children with ISS gained a mean of 1.1 SD over a 3-year period. Their initial height was -2.7 SDS and their final height was -1.6 SDS.

No significant differences were found for psychological benefits when a treated group (of children with the entire range of disorders) was compared with a control group of ISS patients.

Other studies of psychological outcomes reported conflicting results.

Adverse events were not viewed to be a substantial consequence of the treatment.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). The Index of Health related Quality of Life
(IHQL) was used in the valuation of utilities for children with the target disorders. The authors stated that the greatest
QALY gain from treatment (within the treatment period) would be approximately 0.1 and the least gain would be a loss
of QALY of 0.1. Given that treatment is given from an average age of 10 years, for approximately 4 to 6 years, the
authors proposed that children would gain 0.5 QALYs in the best scenario and would lose 0.5 QALYs in the worst
scenario.

**Direct costs**
The UK NHS cost was included in the analysis. The projected annual cost of growth hormone treatment for a 9-year-
old child with GHD was calculated from a published source, using a resource use dosage rate of 15 units/m2 per week
at 1995 prices. Children with TS, CRF and ISS were reported to require double this dose, and all patients would require
increased dosages at the onset of puberty. The resource quantities and the costs were not reported separately, but the
cost and resource use per patient were recorded. Discounting was not reported.

**Statistical analysis of costs**
The cost data were deterministic.

**Indirect Costs**
In line with the perspective of the economic analysis, the indirect costs were not considered.

**Currency**
UK pounds sterling (GBP).

**Sensitivity analysis**
There was no formal sensitivity analysis. However, the potential cost of treating all children with GHD and CRF, along
with the prospect of supplying treatment on demand to all children with short stature in the South and West regions of
the UK, was explored.

**Estimated benefits used in the economic analysis**
The authors reported that the best scenario in terms of benefit was 1.5 more QALYs when assuming 15 years of benefit
(5 of which were in the treatment period), and 5.5 more QALYS when assuming 55 years of benefit (5 of which were
in the treatment period).

**Cost results**
The annual average cost of treating a 9-year-old child with GHD was reported to be approximately 7,000, based on the
lower dose regimen.

The approximate cost for a 9-year-old child with TS, CRF or ISS would be 14,000.

**Synthesis of costs and benefits**
The (best scenario) cost per QALY for children with GHD was reported to be between 5,700 and 20,800.

The cost per QALY for children with TS, CRF and ISS was between 11,400 and 41,700 (assuming between 15 and 55
years of benefit).

**Authors' conclusions**
Growth hormone treatment should be recommended for children with short stature associated with growth hormone
deficiency, Turner's syndrome (TS) and chronic renal failure (CRF). There is currently insufficient evidence to support the use of this treatment in children with idiopathic short stature (ISS). The few studies examining psychological benefits of the treatment presented conflicting results.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was provided for the study of the growth hormone drug, it would appear to represent the standard licensed treatment for GHD, CRF and TS in the UK. The comparison with no treatment permitted the evaluation of the active value of the treatment drug. You should decide if this represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
Although the authors cited a search strategy for the review of the literature, it was unclear whether the remainder of the process was conducted systematically so as to minimise potential biases. The "best quality" evidence was derived on the basis of grading the studies according to specific criteria. The usefulness of these criteria in terms of ascertaining validity is likely to be limited. Although some RCTs were included, the majority of the studies were of weaker designs. Given that some studies lacked a control group, the authors acknowledged difficulties in assessing a direct causal relationship between treatment and outcome in some cases. In addition, the authors also acknowledged that the comparison of height gain results was hampered by differences in the outcome measures used across the studies. All of the above represent substantial threats to the reliability of the results.

Validity of estimate of measure of benefit
The measure of benefit used for the utility analysis was the IHQL, based on an estimate. Although no further references were cited in relation to the validity of this measure, the authors quantified the methods and parameters employed in the analysis of the target disorders.

Validity of estimate of costs
The cost analysis was based on a conservative estimate, which included only the average cost of GHD treatment from the perspective of the UK NHS. Monitoring costs were not included, nor was the extra cost of growth hormone treatment at puberty. An appropriate extrapolation of the costs (based on the higher projected resource use) was presented for patients with CRF and TS. The resource quantities and the costs were not reported separately, although the costs and resource use per patient (based on a reliable source) were recorded. This might not allow the analysis to be easily reworked for other settings. The price year was reported, which will aid any future reflation exercise. However, there was no sensitivity analysis to explore any variation in the costs. Discounting was not reported, although it was potentially relevant given the timeframe of some of the studies.

Other issues
The results are generalisable to the UK NHS. However, the authors did not directly compare their findings with other studies, nor did they directly address the issue of generalisability to other settings beyond the South and West regions.

Implications of the study
The authors suggested that, given the high cost of growth hormone treatment, future good-quality controlled trials with longer follow-up are needed to reliably determine the benefits of such treatment. In addition, more research is required to address the motivation for, and expected benefits arising from, the use of growth hormone treatment.

Source of funding
None stated.
Bibliographic details

Indexing Status
Subject indexing assigned by CRD

MeSH
Child, Preschool; Cost-Benefit Analysis; Fetal Growth Retardation; Growth Hormone /adverse effects /economics /therapeutic use; Humans; Infant, Newborn; Infant, Small for Gestational Age; Insulin-Like Growth Factor I

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